

**AMENDMENTS TO THE CLAIMS:**

This listing of claims will replace all prior versions, and listings, of claims in the application:

**LISTING OF CLAIMS:**

Claim 1. (Currently Amended) Composition intended for the implementation of a cytotoxic treatment in mammals, comprising:

(i) a nucleic acid sequence encoding all or part of an MIP chemokine or a natural variant of MIP1 $\alpha$  or MIP1 $\beta$ ,

(ii) at least one nucleic acid sequence encoding IL-2,  
said nucleic acid sequences being placed under the control of the elements required for their expression in a host cell of said mammal;

wherein the compound is directly administered via a vector or a mixture of vectors expressing both IL-2 and a MIP chemokine;

and wherein the IL-2 and MIP chemokine work together synergistically.

Claims 2-6. (Canceled)

Claim 7. (Currently Amended) The composition according to Claim 1, comprising in (ii) at least two nucleic acid sequences encoding interleukin-2 (IL-2) and all or part of interferon gamma (IFN- $\gamma$ ).

Claim 8. (Withdrawn) Composition according to Claim 4, wherein said polypeptide has at least a cytotoxic activity selected from the group consisting of thymidine kinase activity, purine nucleoside phosphorylase activity, guanine phosphoribosyl transferase activity and cytosine deaminase activity.

Claim 9. (Withdrawn) Composition according to Claim 8, wherein said polypeptide has at least Cdase activity and UPRTase activity.

Claim 10. (Withdrawn) Composition according to Claim 4, wherein said polypeptide having cytotoxic activity is an anti-angiogenic protein factor selected from the group consisting of angiostatin, endostatin, platelet factor PF4, thrombospondin-1, PRP, VEGF, metalloproteases and urokinase.

Claim 11. (Previously Presented) Composition according to Claim 1, wherein said nucleic acid sequences (i) and (ii) are inserted into a recombinant vector of plasmid or viral origin.

Claim 12. (Previously Presented) Composition according to Claim 11, wherein said nucleic acid sequences (i) and (ii) are inserted into the same recombinant vector.

Claim 13. (Previously Presented) Composition according to Claim 11, wherein said nucleic acid sequences (i) and (ii) are inserted into distinct recombinant vectors.

Claim 14. (Previously Presented) Vector comprising:

- (i) a nucleic acid sequence encoding MIP1 $\alpha$ , MIP1 $\beta$  chemokine or a natural variant of MIP1 $\alpha$  or MIP1 $\beta$ , and
- (ii) at least one nucleic acid sequence encoding IL-2,

said nucleic acid sequences being placed under the control of the elements required for their expression in a host cell.

Claim 15. (Previously Presented) Vector according to Claim 14, wherein it is a viral vector.

Claim 16. (Withdrawn) Viral particle comprising a vector according to Claim 15.

Claim 17. (Withdrawn) Method for preparing a viral particle according to Claim 16, wherein:

- (i) introducing a viral vector according to claim 15 into a cell capable of producing said vector, so as to obtain a transfected cell,

(ii) culturing said transfected cell under suitable conditions in order to allow the production of said viral particle, and

(iii) recovering said viral particle from the cell culture.

Claim 18. (Withdrawn) Composition intended for the implementation of a cytotoxic treatment in mammals, comprising:

(i) all or part of an MIP polypeptide,

(ii) all or part of a polypeptide having at least cytotoxic activity,

according to which said polypeptides (i) and (ii) are as defined in Claim 1.

Claim 19. (Currently Amended) Formulation intended for the implementation of a cytotoxic treatment in mammals, comprising ~~a~~ the composition according to Claim 13; or Claim 1, and a support which is pharmaceutically acceptable.

Claim 20. (Previously Presented) Formulation according to Claim 19, comprising capable of being transformed into a cytotoxic molecule by a polypeptide having at least cytotoxic activity.

Claim 21. (Withdrawn) Formulation according to Claim 20, wherein said prodrug is 5-fluorouracil (5-FU) or 5-fluorocytosine (5-FC).

Claims 22-23. (Canceled)

Claim 24. (Previously Presented) A method for treating a proliferative disease in a patient in need, said method comprising administering an effective amount of the composition of Claim 1 by direct administration into an accessible tumor or at its periphery.

Claim 25. (Previously Presented) The composition according to claim 13, wherein said recombinant vectors are adenoviral vectors defective for the replication.

Claim 26. (Previously Presented) The vector of claim 15, wherein said viral vector is an adenoviral vector deriving from an adenovirus.

Claim 27. (Previously Presented) The vector of claim 26, wherein said adenoviral vector is defective for replication.

Claim 28. (Previously Presented) The vector of claim 27, wherein said adenoviral vector defective for replication is deleted of the E1 region.

Claim 29. (Previously Presented) The vector of claim 27, wherein said adenoviral vector defective for replication is deleted of the majority of the E1 and of the E4 regions.

Claim 30. (Previously Presented) The vector of claim 28 or 29, further lacking all or part of the E3 region.

Claim 31. (Previously Presented) The vector of claim 15, wherein said viral vector is a poxviral vector deriving from a poxvirus.

Claim 32. (Currently Amended) ~~the~~ The vector of claim 31, wherein said poxvirus is selected from the group consisting of vaccinia virus, MVA and canarypox.

### **REMARKS**

Entry of this Amendment is proper under 37 C.F.R. § 1.116 because the Amendment places the application in condition for allowance for the reasons discussed herein; and does not raise any new issues requiring further search and/or consideration as the amendments amplify issues previously discussed throughout prosecution. Entry of the Amendment is thus respectfully requested.

Claim 1 has been amended herein to recite that the compound is directly administered via a vector or a mixture of vectors expressing both IL-2 and a MIP chemokine, and that the IL-2 and MIP chemokine have a synergistic effect. Claim 7 has been amended to remove reference to a potentially non-elected embodiment. Claim 19 has been amended to recite proper multiple dependency, as suggested by the Examiner. Claim 32 has been amended to correct an issue of capitalization. Basis for these amendments may be found throughout the specification and claims as-filed especially, for example, at pages 29-32 in the Examples and in Figures 1-6. Thus, no prohibited new matter is presented by the present Amendment.

### **Claim Objections**

Claims 7, 19, and 32 are objected to for minor informalities. The Examiner has objected to the recitation in claim 7 of "all or part of interferon gamma (IFN-γ)" as reading on a non-elected embodiment.

Claim 7 has been amended to remove the phrase "all or part of interferon gamma (IFN-γ)". Thus, that this objection has been obviated. Claim 19 has been

amended to recite "the composition according to claim 13 or claim 1". Thus, this objection has been obviated. Claim 32 has been amended to capitalize the first word of the claim. Thus, it is respectfully submitted that this objection has been obviated.

**Rejections under 35 U.S.C. § 103(a)**

Claims 1, 7, 11-15, 19, 20, and 24 remain rejected and claims 26 and 31 stand rejected under 35 U.S.C. § 103(a) as purportedly unpatentable over Bourns *et al.* (U.S. Patent No. 6,287,557) taken with Hobart *et al.* (U.S. Patent No. 5,147,055) and Nakashima *et al.* (*Pharm Res* 13:1896-1901, (1996)).

In order to establish a case of *prima facie* obviousness, three basic criteria must be met: (1) there must be some suggestion or motivation to modify the reference or combine reference teachings, (2) there must be a reasonable expectation of success, and (3) the prior art reference(s) must teach or suggest all of the claim limitations. See M.P.E.P. §2142. Applicants respectfully submit that these criteria have not been met in the present Office Action, in light of the amendments to the claims herein and the remarks set forth below.

Independent claim 1 has been amended herein to recite that the claimed compound is directly administered via a vector or a mixture of vectors expressing both IL-2 and a MIP chemokine, and that the IL-2 and MIP chemokine have a synergistic effect.

Boursnell *et al.* disclose a therapeutic strategy which involves immunomodulatory genes. In particular, Boursnell *et al.* discuss the potential use of immunomodulating molecules, and cite IL-2 and MIP among more than 40 other immunomodulating polypeptides (see column 7, lines 1-14). Therefore, the specific selection of IL-2 together with MIP would represent only 1 out of more than 780 possibilities. Applicants further note that Boursnell *et al.* only disclose combinations involving IL-2, GM-CSF, lymphotactin and/or CD40L (see column 8, lines 55-57).

Hobart *et al.* disclose a method of treating solid tumors, relying on the administration of a plasmid DNA encoding IL-2 formulated with a cationic lipid mixture. There is no disclosure or suggestion in Hobart *et al.* to combine the IL-2-expressing vector with a gene which codes for the MIP chemokine.

Nakashima *et al.* disclose a method of treating tumors relying on the administration of a plasmid DNA encoding MIP1 $\alpha$ . As with Hobart *et al.*, the disclosure of Nakashima *et al.* is very limited. Nakashima *et al.* fail to provide any reasonable suggestion to link the therapeutic effect provided by the MIP1 $\alpha$ -expressing vector to an IL-2-encoding sequence, and to then utilize the IL-2 and MIP co-expressing vector *in vivo* for treating tumors.

Thus, the cited references, either alone or in combination, neither teach nor suggest the claimed elements of the present invention. In particular, Boursnell *et al.* do not disclose or suggest the specific combination of IL-2 and MIP-encoding nucleotide sequences as claimed in the present invention. The skilled artisan, upon reviewing Boursnell *et al.*, would have a 1 out of 780 chance of selecting the IL-2

and MIP combination. Therefore, such a combination would not have been obvious to the skilled artisan without clear motivation. Hobart *et al.* and Nakashima *et al.* do not remedy the deficiencies of Bournsnel *et al.*, because these references neither teach nor suggest to the skilled artisan to combine MIP- and IL-2-encoding nucleotide sequences.

Applicants further note the synergistic antitumoral protection provided by the claimed invention, via combining MIP- and IL-2-encoding nucleotide sequences. Applicants refer the Examiner to Example 2 of the present specification, on pages 30-31, which illustrates that the administration of a recombinant vector driving the expression of both IL-2 and MIP significantly inhibits the growth of an established tumor and enhances the survival rates of the treated animals. The antitumor protection provided by IL-2 and MIP has been shown for three different tumor models, B16F0 (Figures 1 and 2), RENCA (Figures 3 and 4) and P815 (Figures 5 and 6), respectively. Thus, the introduction of either IL-2 gene or a MIP gene alone does not provide the same degree of therapeutic effect against tumors, as that provided by a vector co-expressing MIP and IL-2 genes. As noted above, claim 1 has been amended herein to specifically recite the coadministration of both proteins in a vector, and the resulting synergistic effect.

Thus, the present invention is patentable over the cited references, and Applicants respectfully request that the rejection be withdrawn.

Claims 1, 11, 13-15, and 25-30 stand rejected under 35 U.S.C. § 103(a) as purportedly unpatentable over Bournnell *et al.* (U.S. Patent No. 6,287,557) taken with Hobart *et al.* (U.S. Patent No. 5,147,055) and Nakashima *et al.* (*Pharm Res* 13:1896-1901, (1996)) in further view of Bruder *et al.* (U.S. Patent No. 6,440,944). Applicants respectfully traverse.

The Office Action states that the cited references, coupled with Bruder *et al.*, disclose of an adenovirus whose E1 region has been replaced or which is deficient for E1, E3, and E4. However, Applicants note that there is no motivation to combine the teachings of Bruder *et al.* with the cited references because Bruder *et al.* are concerned only with the use of this invention in skeletal muscle.

Bruder *et al.* relate to recombinant adenoviral vectors and describe more particularly a E1- and E3-deleted adenoviral vector with a gene expression cassette encoding the reporter gene product  $\beta$ -galactosidase inserted in replacement of the E1 vector (see Figure 1). As described in column 2, line 65, Bruder *et al.* is directed to "targeting a gene product to a particular muscle of an animal." Additionally, rather than the simply targeted administration of the current claims, Bruder *et al.* require that the application of the adenoviral vectors be preceded by either the induction of systemic neutralizing antibodies to the gene transfer vector, or application of an adenovirus which does not contain the gene of interest to the muscle 7 days prior to the application of the genetically relevant adenovirus. None of the claims or examples describe a process in which the adenovirus is simply administered, nor do they suggest the use of such an adenovirus vector for cancer treatment.

Furthermore, Bruder *et al.* disclose the use of an empty (non-expressing) adenovirus vector or an adenoviral antigen that is administered prior to the therapeutic adenovirus in order to induce a systemic immunity. As a result, the therapeutic adenoviral vectors which escape the injected muscle are neutralized by the antibodies circulating throughout the animal, thus limiting the expression of the recombinant gene to the injected muscle.

In addition, Applicants note that the therapeutic molecules that are potentially useful to treat muscle diseases are different from the ones that can be utilized in tumor treatment. Thus, a combination of IL-2 and a MIP chemokine would be of no use for the therapeutic applications contemplated by Bruder *et al.*, *i.e.*, treatment of muscle diseases. As mentioned in column 4, lines 54-60, "An example of this is vascular endothelial growth factor (VEGF protein), which mediates vascular growth. While vascular growth is desirable in the heart to repair damaged cardiac muscle, growth outside the heart can lead to severe problems, including blindness, and increased aggressiveness of tumor cells."

Finally, Applicants note that as amended herein, the present invention recites a synergistic effect provided by the combination of nucleotide sequences encoding IL-2 and a MIP chemokine and not to the vector system used to deliver and express these gene products *in vivo*. In fact, the present invention is readily adaptable to various types of vectors.

Claims 14, 15, 31, and 32 stand rejected under 35 U.S.C. § 103(a) as purportedly unpatentable over Bournnell *et al.* (U.S. Patent No. 6,287,557) taken with Hobart *et al.* (U.S. Patent No. 5,147,055) and Nakashima *et al.* (*Pharm Res* 13:1896-1901, (1996)) in further view of Gruber *et al.* (U.S. Patent No. 6,410,326). Applicants respectfully traverse.

Gruber *et al.* relate to retroviral vectors and means of producing complementing retroviral proteins in cultured cell lines using non-retroviral vectors such as adenovirus and vaccinia virus. Applicants submit that the technical teachings of Gruber *et al.* are limited to the *in vitro* production of proteins of interest using non retrovirus vector systems. Moreover, Gruber *et al.* fail to disclose or even suggest the use of vaccinia virus for expressing antitumor gene products such as IL-2 and a MIP chemokine. There is no suggestion in Gruber *et al.* that such vectors could work *in vivo* in cancer therapy. Thus, this reference fails to remedy the deficiencies of the other references, as discussed above.

Thus, Applicants submit that there is no motivation to combine teachings of the references because none of the cited references teach or suggest to the skilled artisan that one could use nucleotide sequences encoding IL-2 and a MIP chemokine in combination, a reasonable expectation of success has not been provided in the cited references because they fail to establish that such vectors could work *in vivo* in cancer therapy, and the claimed composition is unexpectedly more successful against tumor as compared to vector expressing either protein

individually. Applicants respectfully request that the rejections under 35 U.S.C. §103 be withdrawn.

**CONCLUSION**

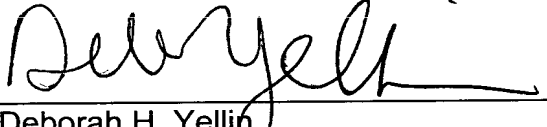
Based on the foregoing, this application is believed to be in condition for allowance. A Notice to that effect is respectfully solicited. However, if any issues remain outstanding after consideration of this Amendment and Reply, the Examiner is respectfully requested to contact the undersigned so that prosecution may be expedited.

Respectfully submitted,

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